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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/088,502	03/28/2002	AKIRA MORIGUCHI	221045US0PCT	2405

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EXAMINER	
SWOPE, SHERIDAN	

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 04/21/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/088,502	MORIGUCHI ET AL.	
	Examiner	Art Unit	
	Sheridan L. Swope	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 February 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) *1,4,6,7 and 9-15* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2,3,5,8 and 16-20* is/are rejected.

7)☒ Claim(s) *8* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *March 28, 2002*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's election with traverse of Group III, Claim 8, in the response of February 18, 2004, is acknowledged. The traversal is on the ground(s) that the Groups all relate to plasminogen activators. Furthermore, Applicants state that a search for one group would overlap and encompass a search for the other Groups and that there is no demonstration that a search for all Groups would be a serious burden to the Examiner.

This is not found persuasive. It is acknowledged that the technical feature linking Groups I-VII is that they all relate to plasminogen activators. However as stated in the Restriction Requirement, Groups I-VII do not relate to a single general inventive concept; they share no special technical feature, as defined by PCT Rule 13.2, because plasminogen activators are known in the Art. In fact, Applicants acknowledged that the inventions defined by the claims are distinct and independent (pg 6, parg 5, line 1). Searching Group III would not encompass searching Groups I, II, and IV-VII and searching all Groups would be a burden on the Office. The requirement is still deemed proper and is therefore made FINAL.

Applicant's amendment of Claims 2, 3, and 5 and addition of New Claims, 16-20 is acknowledged. Claims 1, 4, 6, 7, and 9-15 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to nonelected Inventions, there being no allowable generic or linking claim. Claims 2, 3, and 5, as amended are considered to be within the scope of the elected invention. Claims 2, 3, 5, 8, and 16-20 are examined on their merits.

Specification-Objections

The title is objected to. The words new or novel are not appropriate in the title of a patent, as all patented inventions are assumed to be novel. In addition, the title provides no insight into the subject of the disclosure. Correction is required.

The abstract is objected to. Title pages of prior publications are no longer accepted. A separate sheet, containing only the abstract, should be submitted.

The specification is objected to for poor grammar and spelling. For example, on page 2, line 1-2, the phrase –..."plasminogen activator" should not be limited and be considered to mean...– is unclear. The same problem occurs in paragraph 2 of page 2. In paragraph 2 of page 2, the use of –any one– and –the one– is objected to. On page 14, parg 2, line 3, –plasmine– should be –plasmin–. The specification should be checked and any spelling and grammar problems corrected.

Claims-Objections

Claim 8 is objected to for the following reasons.

The phrase –in sequential use– after the phrase –simultaneously– does not follow parallel sentence construction. Said phraseshould be changed to –sequentially–.

On line 2, –a effective amount of a plasminogen activator–should be changed to –an effective amount of a plasminogen activator–.

Claim Rejections - 35 USC § 112-Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 2, 3, 5, 8, and 16-20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In Claim 8, the phrase –separately– on line 3 is indefinite in view of the prior phrase – administering an effective amount of a plasminogen activator and an effective amount of IL-2 inhibitor–. For purposes of examination, it will be assumed that Claim 8 is meant to recite – simultaneously or sequentially–.

Claims 2, 3, 5, and 16-20, as dependent on Claim 8, are rejected under 35 U.S.C. 112, second paragraph for the same reasons.

Claim Rejections - 35 USC § 112-First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

In this regard, the application disclosure and claims are compared per the factors indicating in the decision re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). These factors are considered when determining whether there is sufficient evidence to support a description that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is undue. The factors include but are not limited to: (1) the nature of the invention; (2) the breath of the claims; (3) the predictability or unpredictability of the art; (4) the amount of direction or guidance presented; (5) the presence or absence of working examples; (6) the quantity of experimentation necessary; (7) the relative skill of those skilled in the art.

Each factor is here addressed on the basis of comparison of the disclosure, the claims, and the state of the prior art in the assessment of undue experimentation.

Claims 2, 3, 5, 8, and 16-20 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating stroke, cerebral infarction, head injury, cerebral hemorrhage, cerebral thrombosis, cerebral embolism, and transient ischemic attacks with the combination of t-PA and FK506, does not reasonably provide enablement for preventing or treating any cerebral neurodegenerative disease in any individual by administering any plasminogen activator and any IL-2 inhibitor. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claims 2, 3, 5, 8, 16, and 17 are so broad as to encompass preventing or treating any cerebral neurodegenerative disease. Claim 19 is so broad as to encompass preventing or treating any hypertensive encephalopathy, Alzheimer's disease, Huntington's disease, Parkinson's disease, and ALS. Claims 2, 3, 5, 8, and 16-20 are so broad as to encompass preventing or treating any cerebral neurodegenerative disease using any plasminogen activator and/or any IL-2 inhibitor. The scope of each of these claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of cerebral diseases to be prevented or treated, the large population of individuals to be potentially treated for prevention of cerebral diseases, the large number of plasminogen activators to be used, and the large number of IL-2 inhibitors to be used. Since the structure of a compound determines its functional properties, predictability of which compounds are plasminogen activators or IL-2 inhibitors and which structural changes in said compounds can be tolerated and retain the desired plasminogen

activator or IL-2 inhibitor activity requires a knowledge of and guidance with regard to which structural aspects, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which each compound's structure relates to its function. However, in this case the disclosure is limited to the plasminogen activator t-PA and the IL-2 inhibitor FK506.

Since the underlying biochemical and cellular problems determine the pathology of a cerebral disease, predictability of which diseases can be treated with the recited method requires a knowledge of and guidance with regard to which biochemical and cellular problems are affected by plasminogen activators and/or IL-2 inhibitors and a detailed knowledge of the ways in which said activators and inhibitors relate to the biochemical and cellular mechanisms underlying any cerebral disease. However, in this case the disclosure is limited to treatment of stroke, cerebral infarction, head injury, cerebral hemorrhage, cerebral thrombosis, cerebral embolism, and transient ischemic attacks.

Techniques for determining the biochemical and cellular mechanisms underlying any cerebral disease, for synthesizing and testing compounds for plasminogen activator and IL-2 inhibitor activity, and for testing said compounds in *in vivo* models of transient focal ischemia, such at middle cerebral artery (MCA) occlusion, are all known. However, it is not routine in the art to determine whether the mechanisms underlying any cerebral disease are relevant to treatment with the combination of a plasminogen activator and an IL-2 inhibitor. It is also not routine to synthesize and test any compound for plasminogen activator or IL-2 inhibitor activity or to test all said compounds in *in vivo* models of any cerebral disease. The number of cerebral diseases to be treated or prevented with a reasonable expectation of success using the recited

method is limited and the results of treating any disease with said method is unpredictable. Furthermore, the number of compounds that can be made or modified with a reasonable expectation of success in obtaining the desired plasminogen activator or IL-2 inhibitor activity are limited and the results of such modifications are unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given plasminogen activator or IL-2 inhibitor to diminish with each further and additional modification.

The specification does not support the broad scope of Claims 2, 3, 5, 8, 16, and 17, which encompasses preventing or treating any cerebral neurodegenerative disease. The specification does not support the broad scope of Claim 19, which encompasses preventing or treating any hypertensive encephalopathy, Alzheimer's disease, Huntington's disease, Parkinson's disease, and ALS. The specification does not support the broad scope of Claims 2, 3, 5, 8, and 16-20, which encompasses preventing or treating any cerebral neurodegenerative disease using any plasminogen activator and any IL-2 inhibitor.

The specification does not support the broad scope of Claims 2, 3, 5, 8, and 16-20, because the specification does not establish: (A) the population of individuals to be treated with the recited method in order to prevent any cerebral disease; (B) the identity of which cerebral diseases, other than stroke, cerebral infarction, head injury, cerebral hemorrhage, cerebral thrombosis, cerebral embolism, and transient ischemic attacks, can be treated with the recited method; (C) the identity of any plasminogen activators, other than t-PA, that can be used in the recited method; (D) the identity of any IL-2 inhibitor, other than FK506, that can be used in the recited method and, in fact, Sharkey et al, 1994 (Fig 3A) and Yagita et al, 1996 (Fig 1 & 2) teach away from the use of cyclosporin A, as recited in Claim 16; (E) the regions of t-PA and FK506

which may be modified without effecting the plasminogen activator and IL-2 inhibitor activity, respectively; (F) the general tolerance of the activity of t-PA and FK506 to modification and extent of such tolerance; (G) a rational and predictable scheme for (i) choosing which population of individuals to be treated with the recited method in order to prevent any cerebral disease, (ii) identifying which cerebral diseases can be treated with the recited method, (iii) identifying which compounds can be used in the recited methods as plasminogen activators or IL-2 inhibitors, and (iv), identifying which regions of t-PA and FK506 can be modified without affecting their activity; and (H) the specification provides insufficient guidance as to which of the essentially infinite possible choices of (i) populations of individuals to be treated to prevent cerebral disease, (ii) cerebral diseases to be treated with the recited methods, and (iii) compounds to be used in the recited methods that are likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including preventing or treating any cerebral neurodegenerative disease in any individual by administering any plasminogen activator and any IL-2 inhibitor. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of the identity of individuals to be treated, diseases to be treated, and compounds to be used is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Claims 2, 3, 5, 8, and 16-20 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to

reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

These claims are directed to a genus of methods for treating or preventing a genus of neurodegenerative diseases in a genus of individuals using a genus of plaminogen activators in combination with a genus of IL-2 inhibitors. The specification teaches treatment of only a single type of neurodegenerative disease, teaches no examples of which individuals to treat to prevent any neurodegenerative disease, and teaches only one combination of plaminogen activator and IL-2 inhibitor to be used in the recited method. Moreover, the specification fails to describe any other representative species of said genus of methods by any identifying characteristics or properties other than treatment or prevention of any neurodegenerative disease in any individual using a combination of any plaminogen activator and any IL-2 inhibitor. Given this lack of description of representative species encompassed by the genus of the claim, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicants were in possession of the claimed invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 2, 3, 5, 8, and 17-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over NINDS, 1995 in view of Bundick et al, 1992 (IDS) and Mori et al, 1997 and further in view of Sharkey et al, 1994 or Kelly et al, 1997 (IDS) as evidenced by Steiner et al, 1998. The report

by the NINDS in 1995 demonstrated that treatment with t-PA within three hours of the onset of ischemic stroke improved clinical outcome at three months. The NINDS do not teach combination therapy with t-PA and an IL-2 inhibitor. Both Bundick et al and Mori et al teach that the macrolide tacrolimus, FK506, is an IL-2 inhibitor. Bundick et al teach that FK506 inhibits production of IL-2 (Fig 2B), while Mori et al, teach that FK506 inhibits the action of IL-2 to induce IL-5 synthesis (Fig 2). Both Sharkey et al (Fig 1A) and Kelley et al (Col 6, lines 24-67) teach that FK506 is a neuroprotective agent in *in vivo* models of focal cerebral ischaemia. Combination treatment with t-PA and neuroprotective agents had been suggested in the art. For example, Steiner et al clearly state that "...combination therapy with thrombolytic and neuroprotective agents may provide additional benefits to those that can be achieved using the individual agents alone." (Abstract; and see especially pg 5, parg 6-pg 6, parg 1). Therefore, it would have been obvious to a skilled artisan to combine therapy with the thrombolytic agent t-PA, as taught by the NINDS, with the neuroprotective IL-2 inhibitor FK506, as taught by Sharkey et al and Kelley et al, in order to enhance treatment of cerebral diseases involving ischemia, such as stroke. Motivation to do so is provided by Steiner et al, as described above. The expectation of success is high, as treatment with t-PA or FK506 alone is known in the art and, furthermore, combination therapy using t-PA and other neuroprotective agents has been successful (see Steiner et al, pg 6, parg 2-3 for review). Therefore, Claims 2, 3, 5, 8, and 17-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over NINDS, 1995 in view of Bundick et al, 1992 (IDS) and Mori et al, 1997 and further in view of Sharkey et al, 1994 or Kelly et al, 1997, as evidenced by Steiner et al, 1998.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sheridan L. Swope whose telephone number is 571-272-0943. The examiner can normally be reached on M-F; 9:30-7 EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy can be reached on 571-272-0928. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Sheridan Lee Swope, Ph.D.

RELEASED FOR DUTY
PRIMARY EXAMINER
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